UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,335	04/08/2002	Gregor Cevc	2200437.123US1	9531

23483 7590 05/01/2008

WILMERHALE/BOSTON
60 STATE STREET
BOSTON, MA 02109

EXAMINER	
GANGLE, BRIAN J	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
05/01/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

michael.mathewson@wilmerhale.com
teresa.carvalho@wilmerhale.com
sharon.matthews@wilmerhale.com

Office Action Summary	Application No.	Applicant(s)	
	09/890,335	CEVC ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,38,40-66 and 68-79* is/are pending in the application.

4a) Of the above claim(s) *46,49,51-54,56,57,61 and 68-79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,38,40-45,47,48,50,55,58-60 and 62-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/15/2007 has been entered.

The amendment and remarks, filed 2/6/2008 and 4/17/2008, are acknowledged. Claims 37-38, 40-66, and 68-79 are pending. Claims 46, 49, 51-54, 56-57, 61, and 68-79 are withdrawn as being drawn to non-elected inventions. Claims 37-38, 40-45, 47-48, 50, 55, 58-60, and 62-66 are currently under examination.

Claim Rejections Withdrawn

The rejection of claims 37-45, 47-48, 50, 55, 58-60, and 62-67 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn upon further consideration.

The rejection of claims 37 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vaccines comprising tetanus toxoid as the antigen, does not reasonably provide enablement for vaccines comprising an antigen derived from pathogens triggering tetanus, is withdrawn in light of applicant's amendment thereto.

The rejection of claim 37 under 35 USC 112, second paragraph, as being rendered vague and indefinite by the phrase "the penetrant in the form of a minute fluid droplet surrounded by a coating of one or more layers of at least 2 substances that differ by at least a factor of 10 in solubility in a liquid medium," is withdrawn light of applicant's arguments.

The rejection of claim 39 under 35 USC 112, second paragraph, as being rendered vague and indefinite by the phrase "the antigen or allergen are associated with the penetrant," is withdrawn light of applicant's arguments.

The rejection of claim 47 as being rendered vague and indefinite by the phrase "derived from," is withdrawn light of applicant's arguments.

The rejection of claim 50 as being rendered vague and indefinite by the phrase "wherein the concentration of each compound used," is withdrawn in light of applicant's amendment thereto.

The rejection of claims 44, 58, and 69 based on the use of the term "low molecular weight irritant," is withdrawn in light of applicant's amendment thereto.

The rejection of claim 65 as being rendered vague and indefinite by the phrase "pure or purified antigen," is withdrawn light of applicant's arguments.

The rejection of claim 67 as being rendered vague and indefinite by the phrase "at least one injectable dose of an antigen," is withdrawn. The cancellation of the claim renders the rejection moot.

Claim Rejections

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 38-45, 47-48, 50, 55, 58-60, and 62-66 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vaccines comprising tetanus toxoid as the antigen, does not reasonably provide enablement for

vaccines comprising an antigen derived from pathogens triggering tetanus, is maintained for the reasons set forth in the previous office action.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is noted that in the interview of 1/17/2008, there was discussion of the use of the term "transdermal immunogenic composition" to overcome the enablement rejection. Applicant has amended independent claim 37 to recite "transdermal antigenic composition," which overcomes the enablement rejection. However, the dependent claims are still drawn to vaccines and thus contain the same enablement issues previously presented.

Applicant argues:

1. That the claims are enabled for vaccines because the experiments for determining whether an antigen produces protective immunity require only routine experimentation in light of the disclosure in the specification and the knowledge in the art. Applicant asserts that Ellis supports this position because the enablement requirement does not require absolute predictability or certainty when teaching how to make and use an invention.

2. That the specification they have disclosed the species and potential antigens for use in vaccines and have shown how antigens from two of those species (cholera toxin and tetanus toxoid) are used to generate an immune response.

3. That the specification teaches the range of potential antigens that can be used in teh compositions of the claims and that all that is left is for one to obtain the protein from the list provided by the specification, make the composition, and perform challenge experiments using different antigens. Applicant asserts that this is merely exchanging one reagent for another.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, while the enablement requirement does not require absolute predictability or certainty, it does require some predictability. Applicant refers to Ellis' comment that "recombinant vaccines do not always provide the solution to the

problem of prevention," highlighting the "always." However, there is no way to predict whether a given antigen will serve as an effective vaccine. It is well known to those skilled in the vaccine art, that making a vaccine is not simply a matter of picking an antigen. If it were simply a matter of picking an antigen, there would already be vaccines for every disease known to man. Further, merely listing a pathogen in the specification does not provide support for a vaccine against that pathogen. For example, the specification lists HIV and rhinovirus as pathogens the instant vaccine can be used against. However, to date, there is no vaccine against HIV or rhinovirus and some researchers now believe that an HIV vaccine will never be developed.

Regarding argument 2, the specification has shown two species out of a genus that includes *all* pathogenic bacteria, *all* viruses, and *all* parasites. This is hardly representative and one can not possibly extrapolate the results from two toxin vaccines to every infectious disease that affects all humans and animals.

Regarding argument 3, the experiments for determining whether an antigen induces protective immunity are not routine. They require the use of techniques that are well known, but the process itself is not routine. Each candidate antigen must be isolated, identified, produced in various forms, then tested in animal models which often require a great deal of work to develop. Moreover, there are many diseases (e.g. gonorrhea) that lack animal models.

As outlined previously:

Nature of the invention: The instant claims are drawn to a transdermal vaccine that comprises a transdermal carrier, a compound which specifically has or induces cytokine or anti-cytokine activity, and an antigen derived from pathogens triggering tetanus. The claim encompasses all antigens that can be found in, and are expressed by, a *Clostridium tetani* cell, including proteins, cell wall constituents, and the tetanus toxin.

Guidance of the specification/The existence of working examples: The specification discloses, in the examples, challenge experiments using the claimed vaccine wherein the antigen is tetanus toxoid. The specification is devoid of any teaching that any antigen other than the tetanus toxoid provides an effective vaccine against any disease, when administered transdermally. To be a prophylactic composition, the

composition must elicit protective immunity, demonstrable by pathogen challenge experiments in a reasonable model system. The skilled artisan would clearly realize the critical deficiency of this specification with respect to vaccines. There is absolutely no demonstration of protective immunity upon the transdermal administration in any animal model of disease by all of the antigens encompassed by the claims. Therefore it is not clear which of the claimed antigens are capable of generating a protective immune response against a given disease, when administered transdermally.

State of the art: Although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from infection (Chandrashekar *et al.*, US Patent 6,248,329, col. 1, lines 35-41). It is well recognized in the vaccine art, that it is unclear whether an antigen derived from a pathogen will elicit protective immunity. Ellis (Chapter 29 of Vaccines, Plotkin, *et al.* (eds) WB Saunders, Philadelphia, 1998, especially p. 571, paragraph 2) exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies... and thus protect the host against attack by the pathogen."

The specification fails to teach that any of the claimed antigens other than the tetanus toxoid can produce a protective response in the host, as is requisite of a vaccine composition. In view of the lack of support in the art and specification for an effective vaccine comprising the claimed proteins, it would require undue experimentation on the part of the skilled artisan to make and use the vaccine as claimed; therefore the full scope of the claims are not enabled.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be

> patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 37-38, 40-45, 47-48, 50, 55, 58-60, and 62-66 under 35 U.S.C. 103(a) as being unpatentable over Glenn *et al.* (PCT Publication, WO 98/20734, 1998) in view of Paul *et al.* (Vaccine Res., 4:145-164, 1995, IDS filed 12/30/2003), is maintained for the reasons set forth in the rejection of claims 37, 39-45, 47-48, 50, 55, 58-60, and 62-67 in the previous office action.

Applicant argues:

1. Applicant has cited MPEP 716.02(a), *KSR International Co. v. Teleflex Inc.*, No. 04-1350 (U.S. Apr. 30, 2007), and *In re Corkill,* 711 F.2d 1496, (Fed. Cir. 1985), stating that "even in references and/or the knowledge of those of skill in the art teach or suggest all of the limitations of a claim, an obviousness rejection is overcome by a showing of unexpected results" and "evidence showing a greater than expected result is persuasive of nonovbiousness."

2. That Paul teaches transfersome compositions that include bovine serum albumin as the substance that the transfersome is transporting across a barrier, but does not teach or suggest a vaccine composition comprising an antigen or allergen that is transported across a barrier. Applicant further asserts that Paul does not teach or suggest the need for additional compounds to co-stimulate an immune reaction (i.e., a compound that induces cytokine or anti-cytokine activity).

3. That Glenn does not teach or suggest improved protective immunity using the transdermal compositions recited in the claims, and Glenn explicitly distinguishes itself from Paul.

4. That the claimed invention provides unexpected results over what was known in the art – that immunoadjuvants do not necessarily strengthen the immune response when using transdermal immunization. Applicant asserts that Paul explicitly sets forth that co-stimulatory factors did not improve the immune response and teaches that such additional factors were unnecessary to produce an improved protective immune response. Applicant also asserts that they have unexpectedly determined that co-stimulatory factors (i.e., compounds that induce cytokine or anti-cytokine activity) induced an improved protective immune response which increased the survival rate of tested animals.

5. That the references teach away from the claimed invention. Applicant asserts that Glenn and Paul both state that it is not possible to immunize epicutaneously with simple protein or peptide solutions ant that dermally applied liposomal or mixed micellar immunogens are biologically inactive like simple protein solutions.

6. That Glenn and Paul teach away from each other because they have different and contrasting explanations for transdermal immunization. Applicant argues that Paul indicates that transfersomes function as sufficient immunization systems and that Glenn teaches that bAREs are also sufficient immunization systems.

7. That Paul does not demonstrate that the compositions described therein could generate any protective immunity. Applicant argues that Paul tests bovine serum albumin, which is not an infectious agent, and that Paul admits that they have not performed the experiments necessary to show vaccination.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, applicant's assertions are incorrect; neither the MPEP or the cited case law support the statements that "even in references and/or the knowledge of those of skill in the art teach or suggest all of the limitations of a claim, an obviousness rejection is overcome by a showing of unexpected results" and "evidence showing a greater than expected result is persuasive of nonovbiousness." In fact, The ultimate determination of patentability must be based on consideration of the entire record, by a

preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The submission of objective evidence of patentability does not mandate a conclusion of patentability in and of itself. *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987). Although the record may establish evidence of secondary considerations which are indicia of nonobviousness, the record may also establish such a strong case of obviousness that the objective evidence of nonobviousness is not sufficient to outweigh the evidence of obviousness. *Newell Cos. v. Kenney Mfg. Co.,* 864 F.2d 757, 769, 9 USPQ2d 1417, 1427 (Fed. Cir. 1988), *cert. denied*, 493 U.S. 814 (1989); *Richardson-Vicks, Inc., v. The Upjohn Co.*, 122 F.3d 1476, 1484, 44 USPQ2d 1181, 1187 (Fed. Cir. 1997) (showing of unexpected results and commercial success of claimed ibuprofen and pseudoephedrine combination in single tablet form, while supported by substantial evidence, held not to overcome strong *prima facie* case of obviousness).

Regarding argument 2, it is noted that claim 37 does not require a vaccine composition, but rather, an antigenic composition. In addition, Paul states "we have used bovine serum albumin labeled with fluorescein isothiocyanate (BSA-FITC) to test an astoundingly new possibility for *in vivo* immunization: vaccination with the full-size proteins across the intact skin" (page 146, paragraph 3). This is clearly a teaching of a vaccine composition comprising an antigen or allergen. The only difference between the elected invention and the composition of Paul is that the composition contains bovine serum albumin rather than tetanus toxoid and IL-12. However, as applicant has argued in previous remarks, "one of skill in the art can practice the invention by merely exchanging one antigen for another." In addition, on page 19 of their current remarks, applicant states "Paul explicitly sets forth that co-stimulatory factors did not improve the immune response, and teaches that such additional factors were unnecessary to produce an improved, protective immune response." On page 20 of their current remarks, applicant states "This indicates that transfersomes function as sufficient immunization systems." As "immunization" means "to render immune," it appears that applicant believes that Paul teaches a vaccine composition.

With regard to applicant's assertion that Paul does not teach or suggest the need for additional compounds to co-stimulate an immune reaction, Paul states "immunoadjuvants thus improve the reproducibility of the transdermal immunization significantly and also minimize the antigen dose effects" (page 155, paragraph 3). Paul also states "the effect of adjuvants is relatively more important for the sparsely dosed immunogens" (page 154, paragraph 4). Thus, Paul provides a strong suggestion that an adjuvant should be included in their composition. While a given adjuvant might not strengthen the immune response, it does serve other purposes. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Where the prior art provides other motivation to select a particular species or subgenus, a showing of a new use may not be sufficient to confer patentability. See *Dillon*, 919 F.2d at 692, 16 USPQ2d at 1900-01. Finally, see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 (U.S. Apr. 30, 2007), "the problem motivating the patentee may be only one of many addressed by the patent's subject matter. The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill n the art. Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed."

Regarding argument 3, the examiner agrees with applicant's assertion. Glenn does not teach the transdermal composition recited in the claims. However, it was not cited for this purpose. Paul teaches transfersomes as an effective transdermal immunization means. Paul lacks the inclusion of tetanus toxoid and IL-12 in the transfersomes. Glenn teaches a transdermal vaccine containing tetanus toxoid and IL-12. Any number of references could have been cited to teach IL-12 as an adjuvant and tetanus toxoid as a vaccine antigen; these are well known. Glenn was chosen because it suggests transdermal delivery of these.

Regarding argument 4, Paul does not explicitly set forth that co-stimulatory factors did not improve the immune response. Paul states that these do not *necessarily*

strengthen the immune response. Paul only tested lipid A and MDP as adjuvants; no other adjuvants were shown not to strengthen the immune response. Further, even if one were to accept that Paul showed that adjuvants did not strengthen the immune response, this does not mean that one would not have included an adjuvant. As stated above, Paul provides strong motivation to include adjuvants in their composition. The fact that the motivation is different from applicant's does not negate the fact that motivation is present. Also, applicant asserts that they have unexpectedly determined that co-stimulatory factors (i.e., compounds that induce cytokine or anti-cytokine activity) induced an improved protective immune response which increased the survival rate of tested animals. However, there is nothing in the claims that refers to the induction of an improved protective immune response or to increased survival of tested animals. Finally, applicant has shown no evidence that their claimed composition provided unexpected results.

Regarding argument 5, the transfersomes taught by Paul are the same as those claimed. The only difference is the antigen and adjuvant included in the transfersomes. Since transfersomes are not "dermally applied liposomal or mixed micellar immunogens," the fact that Glenn and Paul show one cannot use dermally applied liposomal or mixed micellar immunogens is not relevant. There is no suggestion in either Glenn or Paul that transfersomes are not able to provide transdermal immunization.

Regarding argument 6, the fact that the references describe different and incompatible transdermal delivery systems does not prevent a combination of the references. The examiner is not suggesting that the inventions of Glenn and Paul could be literally combined. The antigen and adjuvant of Glenn could be used in the transfersomes of Paul. There is no incompatibility between the references that would prevent such a combination. Furthermore, the fact that Glenn had a successful system does not teach away from a combination with Paul. MPEP 2123 states that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi,* 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994).

Regarding argument 7, Paul states "we have used bovine serum albumin labeled with fluorescein isothiocyanate (BSA-FITC) to test an astoundingly new possibility for *in vivo* immunization: vaccination with the full-size proteins across the intact skin" (page 146, paragraph 3). This is clearly a teaching of a vaccine composition comprising an antigen or allergen. The only difference between the elected invention and the composition of Paul is that the composition contains bovine serum albumin rather than tetanus toxoid and IL-12. However, as applicant has argued in previous remarks, "one of skill in the art can practice the invention by merely exchanging one antigen for another." In addition, on page 19 of their current remarks, applicant states "Paul explicitly sets forth that co-stimulatory factors did not improve the immune response, and teaches that such additional factors were unnecessary to produce an improved, protective immune response." On page 20 of their current remarks, applicant states "This indicates that transfersomes function as sufficient immunization systems." As "immunization" means "to render immune," it appears that applicant believes that Paul teaches a vaccine composition.

As outlined previously, the instant claims are drawn to a transdermal antigenic composition, comprising: (a) a transdermal carrier comprising a penetrant suspended or dispersed in an aqueous solvent, the penetrant in the form of a minute fluid droplet surrounded by a coating of one or more layers of at least 2 substances that differ by at least a factor of 10 in solubility, the substances forming homoaggregates of one substance and/or heteroaggregates of the at least 2 substances, the average diameter of homoaggregates of the more soluble substance, or the average diameter of the heteroaggregates of the at least 2 substances, being smaller than the average diameter of homoaggregates of the less soluble substance, and/or the more soluble substance solubilizing the droplet and the content of the more soluble substance being up to 99 mol-% of the concentration required to solubilize the droplet or corresponding to up to 99 mol-% of the saturating concentration in an unsolubilized droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounded by the coating is at least 5 times lower than the elastic deformation energy of red blood cells or of a phospholipid bilayer having fluid aliphatic chains; (b) a compound which specifically has

or induces cytokine or anti- cytokine activity; and (c) an antigen or mixture thereof and/or an allergen or mixture thereof. Further limitations include: a vaccine of claim 37 wherein the at least two substances are two ionization states or salt forms of the same substance (claim 38); a vaccine wherein the less soluble substance with the tendency to aggregate is a polar lipid, and the more soluble substance is a surfactant (claim 40); wherein the penetrant is between 30 nm and 500 nm (claim 41); wherein the total weight of droplets in the vaccine for use on human or animal skin is 0.01 weight-% to 40 w-% of total mass (claim 42); wherein total antigen concentration is between 0.001 and 40 w-% of the total penetrant mass (claim 43); comprising a chemical irritant and/or an extract or compound from a pathogen or a fragment or a derivative of the irritant, pathogen compound, or extract (claim 44); wherein the compound is IL-12 (claim 45); wherein the antigen is derived from *Clostridium tetani* (claims 47-48); wherein the concentration of each compound used is up to 1000 times higher than a concentration optimum established in corresponding tests performed by injecting the vaccine or performing the tests *in vitro* (claim 50); wherein the concentration of the compound from a pathogen is between 10 times lower and up to 1000 times higher than the concentration used with the corresponding injected vaccines employing similar antigen (claim 55); wherein the irritant is selected from the group consisting of surfactants and derivatives and combinations thereof (claim 58); wherein the surfactant enhances skin permeation (claim 59); wherein the concentration of the irritant is below by at least a factor of 2 to a factor of 10 or more a concentration which is unacceptable owing to local irritation in tests on the same or a comparable subject (claim 60); wherein the applied dose of the antigen differs by the factor of 0.1 to 100 from the dose which would have to be used with an injection (claim 62); wherein the applied dose of an antigen is less than 10 times higher than the dose which would have to be used with an injection (claim 63); wherein the applied penetrant dose is between 0.1 mg/cm^2 and 15 mg/cm^2 (claim 64); and wherein the antigen is a pure of purified antigen (claim 65). Further claims are drawn to a kit containing the vaccine of claim 37 in a packaged form (claim 66).

Glenn *et al.* disclose a transdermal vaccine that contains tetanus toxoid and interleukin-12 (see abstract; page 16, lines 15-17; and page 18, lines 15-30). Glenn *et al.*

state that the antigens used in the vaccine can be purified (see paragraph bridging pages 15-16).

Glenn *et al.* differs from the instant invention in that the transdermal vaccine does not comprise a carrier wherein the substances forming homoaggregates of one substance and/or heteroaggregates of the at least 2 substances, the average diameter of homoaggregates of the more soluble substance, or the average diameter of the heteroaggregates of the at least 2 substances, being smaller than the average diameter of homoaggregates of the less soluble substance, and/or the more soluble substance solubilizing the droplet and the content of the more soluble substance being up to 99 mol-% of the concentration required to solubilize the droplet or corresponding to up to 99 mol-% of the saturating concentration in an unsolubilized droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounded by the coating is at least 5 times lower than the elastic deformation energy of red blood cells or of a phospholipid bilayer having fluid aliphatic chains.

Paul *et al.* disclose an transdermal vaccine (see page 146, paragraph 3) that comprises a transdermal carrier known as a transfersome that comprises ethanolic soybean phosphatidylcholine, sodium cholate, and an antigen (see page 148, Transfersomes preparation). Said transfersomes have the same composition as the claimed vaccine carrier and would thus necessarily have the same physical and immunological properties as the claimed vaccine transfersomes. Additionally, Paul *et al.* disclose that transdermal immunization using large protein molecules can be accomplished using said transfersomes, and that, if properly optimized, a transdermal drug transfer efficacy of > 90% can be achieved (see page 162, paragraphs 7-8). Paul *et al.* further disclose that vaccination can be accomplished using full size proteins across the intact skin (see page 146, paragraph 3).

It would have been obvious to one of ordinary skill in the art to use the transdermal carrier (transfersomes) of Paul *et al.* in the vaccine of Glenn *et al.* in order to take advantage of the high drug transfer efficacy of transfersomes, as disclosed by Paul *et al.* One would have had a reasonable expectation of success because Paul *et al.* disclose that their transfersomes are capable of delivering full size proteins across the skin in a

vaccination. Regarding claim 38, the transfersomes of Paul include sodium cholate, which is the conjugate base of cholic acid. In all acid-base reactions, the acid will react with a base to form the conjugate base and vice versa, switching ionization states. The dissociation constant of sodium cholate is such that, in the transfersome composition of Paul, there would be two ionization states of sodium cholate. Regarding claim 40, phosphatidylcholine is a polar lipid and sodium cholate is a surfactant. Regarding claims 44 and 58, sodium cholate is a surfactant and therefore and irritant. Regarding claims 41-43, 50, 55, 60, and 62-64, these claims are merely optimized ranges for materials in the vaccine. Paul *et al.* disclose that the vaccine should be properly optimized to achieve efficacy. Further, according to MPEP 2144.05, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Regarding claim 66, the vaccine disclosed by the prior art are packaged in some form, thus anticipating the limitation of a kit containing said vaccine in a packaged form. Therefore, as the vaccine disclosed by the prior art contains a dose of antigen, the prior art anticipates this limitation.

New Claim Rejections

35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38, 40-45, 47-48, 50, 55, 58-60, and 62-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 38, 40-45, 47-48, 50, 55, 58-60, and 62-67 recite the limitation "vaccine." There is insufficient antecedent basis for this limitation in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 37 is rejected under 35 U.S.C. 102(b) as being anticipated by Paul *et al.* (Vaccine Res., 4:145-164, 1995, IDS filed 12/30/2003).

The instant claim is drawn to a transdermal antigenic composition, comprising: (a) a transdermal carrier comprising a penetrant suspended or dispersed in an aqueous solvent, the penetrant in the form of a minute fluid droplet surrounded by a coating of one or more layers of at least 2 substances that differ by at least a factor of 10 in solubility, the substances forming homoaggregates of one substance and/or heteroaggregates of the at least 2 substances, the average diameter of homoaggregates of the more soluble substance, or the average diameter of the heteroaggregates of the at least 2 substances, being smaller than the average diameter of homoaggregates of the less soluble substance, and/or the more soluble substance solubilizing the droplet and the content of the more soluble substance being up to 99 mol-% of the concentration required to solubilize the droplet or corresponding to up to 99 mol-% of the saturating concentration in an unsolubilized droplet, whichever is higher, and/or wherein the elastic deformation energy of the droplet surrounded by the coating is at least 5 times lower than the elastic deformation energy of red blood cells or of a phospholipid bilayer having fluid aliphatic chains; (b) a compound which specifically has or induces cytokine or anti- cytokine activity; and (c) an antigen or mixture thereof and/or an allergen or mixture thereof.

Paul *et al.* disclose an transdermal carrier (see page 146, paragraph 3) known as a transfersome that comprises ethanolic soybean phosphatidylcholine, sodium cholate, an antigen (BSA), and a compound which induces cytokine activity (lipid A) (see page 148, Transfersomes preparation). Said transfersomes have the same composition as the claimed vaccine carrier and would thus necessarily have the same physical and immunological properties as the claimed vaccine transfersomes.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian J Gangle/
Examiner, Art Unit 1645

/Shanon A. Foley/
Supervisory Patent Examiner, Art Unit 1645